

## RECENT HISTORY OF PNEUMONIA

## OSLER CLUB SYMPOSIUM

The 99th meeting of the Osler Club, held in London on January 11, with Mr. ZACHARY COPE in the chair, was devoted to a symposium on pneumonia in Osler's time and since.

## Osler's Fatal Illness

LORD HORDER began by giving an intimate and moving account of Osler's fatal illness. He said that when Harvey Cushing's *Life of Osler* appeared in 1925 he was disappointed to find that in the last few poignant pages the drama of the final stage of Osler's illness had been telescoped into a few apparently casual references. It was on December 12, 1919, that Osler, who was suffering from a prolonged and obscure disease in his chest, sent for him to come to Oxford. It was a shock to see him very ill and emaciated, in a state of extreme toxæmia, and speaking little because speech brought on a bout of paroxysmal coughing. Osler himself had jotted down for his information, in that terse fashion of his, some pencilled comments on his own condition. Seven days previously the chest had been punctured and a little serous fluid drawn off without any relief of symptoms. Lord Horder postulated the presence of an interlobar empyema, and the puncture was repeated, using the longest needle procurable at the time. The same sort of fluid was forthcoming and that only in small amount. The condition remained relatively unchanged for another week, so that he made up his mind that something further should be done by way of exploration. A couple of extra long needles were made, Osler readily agreeing to the exploratory "séance." The first puncture was negative, but the second was successful, and when the stylet was withdrawn Osler himself said, "You've got it, my boy." Between 4 and 5 ml. of stinking pus was withdrawn. On the following day Charles Gordon-Watson drained an abscess cavity. The drainage, never very copious, ceased three days later. No further collection of pus was revealed by a second operation. Four days later the end came in dramatic fashion. He (Lord Horder) had talked with Osler in the morning, and had then gone to lunch downstairs, when the nurse called him quickly, and on going upstairs he found that the dressings and the bed were soaked in blood. The sepsis had opened up the wall of a small vessel in the upper lobe of the lung, and Osler died a few hours later that day.

A study of Osler's last illness threw little if any light on the subject of pneumonia in general. The fact that the pus contained Pfeiffer's bacillus was no more proof that the original disease was an "influenzal pneumonia" than the fact that the onset of the disease occurred during a period of fairly high influenzal incidence. All that could be said was that the disease might well have come into the category of what was to-day called "atypical or virus pneumonia," an unfortunate introduction into the nomenclature. Nor did he much favour the term "pneumonitis," though there was more to be said for it. Even in a severe epidemic of influenza it was more helpful to label the condition "influenza with pneumonia" than to call it "influenzal pneumonia." The critic might ask what a name mattered, but it did matter how words were used, because words determined subsequent thinking. The tendency to stress the lung condition so as to give it a predominant place in the nomenclature was probably due to the fact that, both clinically and histologically, the lung lesions declared themselves while yet the search went on for causative agents in the great majority of virus infections. This tendency should be resisted. With more research and some forbearance the answer would be unfolded.

As long ago as 1887, in an editorial summary of a report on pneumonia in the hospitals of New York and Boston, Osler said that the disease had come to be known as a specifically self-limited disease, and the only rational treatment was the expectant one. He added, however, that to the next generation the symptomatic and expectant plan of treatment then in vogue would appear crude and

unscientific. Osler's prophecy had been fulfilled, and so no doubt would be a further prophecy that the generation next to ours would regard as crude and unscientific the nosology at present used with respect to pneumonias in the textbooks to-day.

## The Advent of the Sulphonamides

Sir LIONEL WHITBY followed with a succinct account of the discovery by Domagk and his assistants at Elberfeld of the anti-streptococcal activity of an azo dye containing a sulphonamide group. Domagk's compound, known as "prontosil," was patented in 1932, but the experimental results were not published until 1935, and these were followed by clinical reports in German literature concerning work which had been going on in the trial period. Prontosil was a water-insoluble basic azo dye (sulphamido-chrysoidin) suitable for oral administration, from which an acid dye known as prontosil soluble was developed. It was early suggested and later proved that this complex molecule of sulphamido-chrysoidin owed most of its virtue to the fact that it was reduced in the body to *p*-aminobenzene-sulphonamide, now known as sulphanilamide.

As a result of a great deal of research there eventually emerged so far as pneumonia was concerned, and in historical order, sulphapyridine (at first known as M. & B. 693), sulphathiazole, sulphadiazine, sulphamezathine, and sulphamerazine. The first of these was synthesized by Ewins and Phillips, of May and Baker, Ltd., and was proved to have great therapeutic value against pneumococcal infections in mice. Clinical confirmation in the human subject soon followed, first in a few cases reported by Telling and Oliver 13 years ago, and then by Evans and Gaisford, who in a Birmingham municipal hospital in that year treated 100 cases of lobar pneumonia with a mortality of no more than 8%, whereas the control series had a death rate as high as 27%. From even this small experiment it was clear that the disease which in the days of Osler could be treated by no more than palliatives, stimulants, sedatives, and careful nursing, and later by a laborious and expensive serum routine, could now be easily and cheaply controlled.

Sir Lionel Whitby gave one or two personal anecdotal recollections of those wonderful years. It was the intrusion of a good dinner which led to the feeding of a batch of mice with sulphapyridine at a rather late and unpopular hour—indeed, well after midnight. This batch was the first to exhibit a survival rate of 100%. Thereafter in all assays the technique was so altered as to contain a night dose, and all who recalled the time when the "sulpha" drugs were used widely for the treatment of pneumonia would remember that this rule was carried out at the bedside with dosage four-hourly day and night.

Sulphapyridine was handicapped by the intense vomiting it caused, which led some who owed their lives to the drug to declare that they would prefer to die rather than endure the treatment again. Thus sulphathiazole, not much more active but far less toxic than sulphapyridine, came to replace the latter as soon as it had been rediscovered. Sulphathiazole was in actual fact found at the same time as sulphapyridine when mouse tests were being carried out, but there was a tendency to pass it over, since in the animal it seemed to have little or no advantage over sulphapyridine—a finding which was due to rapid excretion and therefore low blood concentration.

It might be said as a historical fact that the sulphonamides, from sulphapyridine to sulphamerazine, held the field for the specific treatment of pneumococcal pneumonia until penicillin came to be sufficiently plentiful for everyday use. Even to this day one or other of the potent and relatively non-toxic sulphonamides could still be regarded as an indispensable drug.

## Changing Clinical Aspects

Sir ADOLPHE ABRAHAM said that he was told that the modern medical student rarely saw a case of typical lobar pneumonia. Unhappily a "superannuated physician" had had ample opportunity for such clinical observations. But

was there in fact a remarkable reduction in the present-day incidence of lobar pneumonia? Had the type of case changed, and had the treatment by sulphonamides been responsible for the change? Then what about all this business of virus pneumonia or pneumonitis? He was not in a position to judge. "Old dogs do not learn new tricks." In his view lobar pneumonia received in many circles an entirely wrong nomenclature. He was taught—not by Lord Horder—that pneumonia was a disease of the lungs, a misconception which he had never been able to dispel. Osler rightly put pneumonia in his section of diseases due to bacterial infection; yet modern textbooks of medicine put it among the diseases of the respiratory organs. Pneumonia was no more a disease of the lungs, although respiratory symptoms predominated, than typhoid fever was a disease of the intestines.

During 2½ years in the first world war he (Sir Adolphe Abrahams) saw 558 cases of lobar pneumonia from onset to termination. In nearly every case the disease began with a rigor. Temperature was generally of the order of 102–3° F., rarely higher. The pulse–respiration ratio, upon which clinicians were very emphatic, was raised. Physical signs in 80 or 90% of the cases occurred within the first four days. Physicians with exceptional experience developed a flair for the recognition of early physical signs; they did not wait for such features as dullness at the base or even bronchial breathing, but there was a queer little catch in the breath which they recognized. In only 12 of his cases were physical signs entirely absent throughout the illness. The sputum was generally of the so-called rusty type. In something over 10% of the cases sputum was entirely absent. Other features worth mentioning were herpes, which Hippocrates had observed, and which denoted a good prognosis, abdominal pain (severe in 31 of the 558 cases), and thoracic pain (almost invariable, and not always on the same side as the physical signs, and more frequently on the right than on the left). The mortality had been 10.9%. The only complication of any real significance was empyema, the incidence of which was over 20%. Other complications were pericarditis, meningitis, arthritis occasionally, and, he supposed, infective endocarditis, but these were very few indeed.

As for prognosis, one of the features of lobar pneumonia was that some who were almost moribund recovered and sometimes a comparatively benign case running a good course suddenly collapsed and the patient died. The fact that the only treatment in those days was expectant and symptomatic did not prevent people from trying all sorts of remedies. It was a commonplace for practitioners to write to the medical journals stating that they had been in practice for 20 years and had seen 15 cases of lobar pneumonia all of which had recovered in consequence of a particular treatment. People who used vaccines produced figures which to a certain extent were convincing. In his own series he had at one time 70 consecutive cases without a death. Had he adopted some form of special treatment, the more fantastic the better, the conclusion would have been irresistible that his treatment had had something to do with it. At one time brandy was regarded as a sort of specific. On the other hand, the London Temperance Hospital then gave alcohol only to patients practically moribund, with the result, of course, that their statistics worked out very much to the detriment of alcohol. Oxygen was used, but more for the benefit of relatives than of the patient. But the treatment in those days boiled down to good nursing, fresh air (if he himself had any choice in the matter he had his patients in the open air), and, above all, sedatives to induce sleep. In his experience 70%, he thought, would have recovered whatever was done; between 20 and 30% would have died whatever was done. There remained 5 or 10% in which skilled treatment and nursing might just have turned the scale. He was always impressed by Leonard Williams's dictum that pneumonia was best treated by faith, hope, and charity—faith in *vis medicatrix naturae*, hope for the absence of complications, and charity towards those who differed from you.

### Various Experiences

Sir ALEXANDER FLEMING recalled a senior physician to whom he was once clerk whose chief treatment for pneumonia was ice packs. Unfortunately, he had a junior who did not believe in ice packs and put on poultices—a confusing situation. Sir Alexander was told that they did not see pneumococcal pneumonia in hospital now. Sulphonamides and antibiotics were given outside, and the hospital got only the cases where these agents failed. The cases that came to hospital were sometimes amenable to "aureomycin" or "chloromycetin," and then they were called virus pneumonia. "I do not know what virus pneumonia is, but it is quite a nice name, anyway." Dr. W. R. THROWER, who was associated with the work in the laboratories of May and Baker, gave an account of his first case treated with "693." On May 16, 1938, he was presented with a box of the tablets and forgot about them, but two days later a case of lobar pneumonia in a man aged 45 was presented, and he decided to see what these tablets could do. It was not known how much to give, nor how often, nor how the drug acted. A very tentative start was made by giving 0.5 g. four-hourly. The dose was repeated throughout the night. The next morning the patient was no worse, perhaps better, but by the afternoon there was undoubted improvement. The following morning, which should have been the morning of crisis, the patient was sitting up and asking for food. Mr. G. H. COLT described his own experience as a patient with double pneumonia at the time of the first world war. The great help was nursing. The V.A.D. service, which produced hot meals at all hours of the day and night, helped tremendously.

Dr. ALEXANDER CAWADIAS spoke in appreciation of Lord Horder's insistence on careful nosology and upon the natural history of disease, to borrow a term from Sydenham. The natural history of pneumonia was, of course, first described by Hippocrates. One of the best descriptions in modern times was by the French nosologist Grisolle. Dr. Cawadias agreed with Lord Horder in his objection to the term "influenzal pneumonia." Influenza was in one morbid category and pneumonia in another. Concerning the history of treatment, he mentioned that meted out to an early Empress of Austria in the eighteenth century. It was reported that she had cough, sputum, and pain. The physicians were called in and bled her 3 or 4 pints. She was no better, and they bled again, 5 or 6 pints, and, as there was no improvement, they came next day and bled her again, and it was reported that "notwithstanding the active bleeding, the patient died."

Mr. DICKSON WRIGHT mentioned post-operative pneumonia, of which, he said, there were two kinds, one occurring immediately after operation and the other later. The second was the more serious in its effects. The respiration rate was high, the patient became very toxæmic, and there were mental changes.

The CHAIRMAN (Mr. Zachary Cope) mentioned that he started his career as house-physician to David Needham, who was one of the advocates of ice packs for pneumonia. Needham was a most conscientious physician, and thought there was scientific proof that the pneumococcus did not thrive so well if the temperature was a little lower than that of the body, so that the external application of an ice pack would reduce the temperature inside the chest to the required degree. It was extraordinary that so conscientious and scientific a man should adopt so pseudo-scientific an attitude. Post-operative pneumonia used to be attributed to the anaesthesia, but that was a misplaced judgment, because it had been proved again and again that pneumonia developed even after a local analgesic, when there was no infiltration of any substance into the lungs and the operation did not interfere in any way with the diaphragm.

Mr. Cope added that there were two or three medical evenings which were indelibly imprinted on his memory, and to these would be added the meeting of that evening, with the three brilliant opening addresses, the first of them, full of clinical wisdom, by a man who had just celebrated his 81st birthday.

It was announced that Dr. Carlyle Lyon had presented the Club with certain books, including a volume of the *British Medical Journal* for 1886 which contained some of Osler's earliest writings, his Cartwright lectures on the blood corpuscles.

## MEDICINE IN UGANDA

[FROM A SPECIAL CORRESPONDENT]

The annual clinical conference of the Uganda Branch of the B.M.A., held from December 7 to 9, 1951, in the Makerere Medical School at Mulago Hospital, by courtesy of the dean, was attended by many Uganda members, by representatives from Kenya and Tanganyika, and by visitors from the United Kingdom. The president of the branch, Dr. A. W. WILLIAMS, opened the proceedings with an account of the history of Mulago Hospital and the growth of the medical school.

### History of the Hospital and Medical School

The Government hospital at Mulago, founded in 1913 as a venereal diseases treatment centre, had grown from a collection of mud-and-wattle grass-roofed wards to a 650-bed general hospital, accommodated in pavilion-type wards spreading down the slope of the hill. Proposals for new buildings had twice come to nothing, in 1939 and in 1946, but within the last few months a site had been cleared on which it was hoped a new hospital would be built.

The medical school, which had begun as a departmental training school of the Uganda Government, had admitted its first four students in 1924 under the first medical tutor, H. B. Owen, later principal of the school and medical superintendent of Mulago Hospital. Students from outside Uganda had been admitted in 1930. The course, at first lasting only four years, including premedical studies, without anatomical dissection, midwifery, preventive medicine, or more than the most rudimentary pathology, had developed by stages to a seven-year course with a content similar in all respects to those given in the medical schools of Great Britain. It catered now for students from Kenya, Uganda, Tanganyika, Zanzibar, and Nyasaland, who, on qualifying as holders of the Diploma of Medicine of Makerere College, became medical practitioners licensed to practise in East Africa. Well-equipped preclinical departments and a fine medical library had grown up, and there were now vigorous clinical and pathological departments at Mulago Hospital staffed jointly by members of the Colonial Medical Service and of the Makerere College clinical departments.

In tracing the growth of the hospital and school, Dr. Williams paid tribute to Uganda's voluntary hospital at Mengo and its staff, who under the late Sir Albert Cook had pioneered Western medicine in East Africa; and emphasized the indebtedness of the school to the many Colonial Service medical officers, pathologists, and specialists who had served at Mulago in the last 35 years.

Sir HENEAGE OGILVIE then spoke on the surgeon's part in the fight against cancer, and discussed the place of radiotherapy and chemotherapy in the treatment of malignant disease. In answer to a question whether East Africa should press for a radiotherapy centre, he said that the cost would be high and that he felt that the money could be more usefully spent in other ways.

The president of the Uganda Branch then opened an exhibition prepared by the major pharmaceutical and medical supply firms, the first seen in Uganda, and one which was very much appreciated by those present.

### Indolence or Illness?

A discussion took place on "What are the economically important diseases of Uganda?" Dr. J. M. CALDWELL gave some figures compiled from the returns made by the larger employing concerns in Uganda, and dealt especially with malaria, respiratory disease, tropical ulcer, and injuries

as causes of loss of working hours. Tropical ulcer was a disease of the agriculturist, and in such folk correlated closely with the figures for total injuries, but this was not seen in factory workers. It was regrettable that the largest employer in Uganda, the Government, made no returns. Dr. Caldwell stressed the great importance of respiratory diseases and malaria as causes of morbidity, and Dr. R. G. LADKIN supported this by an analysis of the causes of morbidity in persons attending rural dispensaries in the regions round Kampala. The analysis covered over 250,000 out-patients. He pointed out that attendance at rural dispensaries was the nearest thing to a general-practitioner service available to Africans in Uganda. Although malaria (165/647) was the most frequent cause of admission to beds, in dispensaries it was closely followed by pneumonia (159/647), and as a cause of attendance respiratory diseases far out-topped malaria. Injuries, local infections, and surgical emergencies were the next most frequent conditions, followed by diarrhoea and dysentery, burns, pyomyositis, and gonorrhoea (all in the region of 15-45/647). Arthritis, whooping-cough, and tropical ulcer were the remaining major causes of invalidism. Dr. Ladkin then analysed the factors contributing to the high incidence of pneumonia, and concluded that the incidence was low in sparsely populated rural areas, increased considerably in areas of higher population density, and occurred in epidemic forms in overcrowded areas. It was one of the most important diseases of Uganda.

Mr. PAKENHAM-WALSH, of the Uganda Company, speaking as an employer of African labour, expressed the view that all this information hardly concerned an employer of unskilled African labour. Disease was not a cause of low production. Too much emphasis was now placed on the need to raise the standard of health and living in order to obtain a greater output per day. Since the war, conditions of health, housing, and food had improved and absenteeism had been reduced, but work output had actually fallen. By custom, agricultural work ceased at noon or when the task appropriate to such working hours was completed, and, while disease might make a man slow in completing his task, the healthy man did no more. In a labour force of 850 men in the last 12 months absenteeism from sickness was only 0.9% and absenteeism from other causes was only 1.9% as against 30% before the war, when no food was issued. The more serious diseases of Uganda were indolence, established custom, and lack of economic pressure.

An animated discussion followed these papers. The question of incentives was raised, and one suggestion for reducing invalidism was the supply of cheap waterproof clothing. Mr. Pakenham-Walsh's experience was supported by many present.

### The Absence of "Stress" Diseases

On the following morning a clinic was held by the staff of the medical division of the hospital. Cases were shown by Dr. A. W. Williams, Dr. P. W. Hutton, Dr. A. B. Raper, and Dr. H. C. Trowell.

Dr. J. H. SHELDON then described his experiences with A.C.T.H. and cortisone in clinical medicine, and went on to discuss their relevance to local conditions. He was fascinated by the fact that all the diseases for which they were frequently used in temperate regions, rheumatoid arthritis particularly, were absent or very rare in Uganda. He hoped that research would be directed to the elucidation of the problems presented by this disparity. It seemed that the African response to stress was abnormal; or was it normal and the European reaction abnormal? Did diet play a part? It seemed possible that a deficient diet might not provide the necessary materials for the elaboration of steroid hormones and that the frequency of enlarged adrenal glands in Africans was an indication of an attempt to make good this failure.

### Epidemiology of Schistosomiasis in the West Nile District

Dr. G. NELSON then described his survey of schistosomiasis (Mansoni) in the West Nile district, where the